High Cholesterol Levels Are Associated with Improved Long-term Survival after Acute Ischemic Stroke

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Background: Prior statin treatment and high admission cholesterol have been associated with favorable outcome after ischemic stroke (IS), a paradox not completely explained. The aim of this study was to investigate the effect of admission cholesterol levels and the impact of statin treatment on short- and long-term survival after IS. *Methods:* Consecutive patients admitted in 2006 and 2010 were included in the study. Total cholesterol of 4.6 mmol/L or more was defined as high. Logistic regression analysis was performed to assess predictors of 1-month mortality, and Cox proportional hazard regression analysis was applied to investigate predictors of long-term mortality. *Results:* Of 190 patients included in the final analysis, 21 (11%) died within 1 month and 61 (32%) died during 7 years of observation. Low cholesterol was associated with older age, lower blood pressure (BP), presence of angina, and higher risk of death. Three-month, 1-year, and 5-year survival rates were 100%, 98%, and 84%, respectively, in high cholesterol patients, compared with 92%, 87%, and 57% in low cholesterol group ($P = .0001$ with the log-rank test). Mortality risk was increased for patients with low cholesterol (hazard ratio: 1.97; 95% confidence interval [CI]: 1.05-3.69), after adjustment for age and admission National Institutes of Health Stroke Scale score. After further adjustment for angina and admission BP, the effect of cholesterol on mortality risk was still obvious, yet attenuated (hazard ratio: 1.87; 95% CI: .94-3.32). *Conclusions:* High admission cholesterol may be associated with increased long-term survival after IS. Future studies on the temporal profile of cholesterol levels and stroke outcome would be of interest. **Key Words:** Brain ischemia—stroke—fatal outcome—cholesterol—statins.

Introduction

Ischemic stroke (IS) is a leading cause of death and long-term disability in adults worldwide.[1] One-month mortality rates range from 13% to 27% in Europe,[2] and stroke severity is the most powerful predictor of functional outcome and death.[3] One-year survivors have annual mortality rate near 10% for the following 4 years,[4] and age, severity of stroke, cardiac disease, cardioembolic etiology, hypertension, and diabetes are the most important predictors of long-term outcome.[3] Identification of modifiable predictors of long-term outcome has facilitated the selection of appropriate treatment for secondary prevention to improve prognosis. However, despite available treatment strategies, stroke mortality has not changed dramatically over the last 4 decades.[5]

Treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has been associated with reduced recurrence of IS,[6] reduced vascular events in patients with prior IS, and reduced IS in patients with other vascular disease.[7] An Irish study has recently shown beneficial effect

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of acute statin treatment in survival and functional outcome up to 1 year after stroke.[8] Further exploration of interactions among admission cholesterol levels, previous statin treatment, and stroke morbidity has shown a possible "reverse epidemiology" between lipids and outcome.[9] Earlier studies have also indicated a positive association between elevated admission cholesterol at IS onset and improved short-term functional outcome[10] and 10-year survival.[11] In another study, lower total and low-density lipoprotein (LDL) cholesterol levels were independent predictors of poor 3-month functional outcome in men but not in women.[12]

The aim of this study was to further investigate the effect of cholesterol levels and the impact of statin treatment in short- and long-term survival after acute IS.

Methods

Study Design and Population

The study was approved by the Local Ethics Committee. The Karolinska University Hospital in Huddinge is a hospital of reference with approximately 800 beds, serving an ethnically diverse population of around 250,000 persons. We aimed to design a hospital-based register on cerebrovascular diseases based on a standardized protocol including demographic characteristics, vascular risk factors, comorbidities, clinical investigation results, biochemical and neuroimaging data, complications, and outcome. Since 2006, all medical records including previous and current medication and laboratory results are digitalized. Our study was designed as a retrospective, hospital-based, follow-up cohort including all patients admitted in the stroke unit since January 2006. During the initial, pilot phase of patient recruitment, we enrolled 220 patients admitted during 2006 and 120 patients admitted in 2010, to investigate the differences in management of hyperglycemia and their impact on outcome after IS (Nilsson U, Kostulas K, Markaki I, Sjöstrand C, unpublished data). Of 340 patients initially enrolled in this pilot, 37 were excluded because of nonvascular diagnosis (n = 20) or because of admission later than 72 hours from symptom onset (n = 17). Patients with vascular diagnosis other than IS (n = 190) or transient ischemic attack (n = 52), including hemorrhagic stroke (n = 49), transient global amnesia (n = 4), large-vessel dissection without evidence of IS (n = 5), vasculities (n = 2), and sinus thrombosis (n = 1) were also excluded. A total of 190 IS patients were included in the current analysis. Age, gender, etiologic phenotypes, risk factor, and biochemical profile and treatment options on admission and at discharge did not differ significantly between patients admitted in 2006 compared with patients admitted in 2010.

Data Collection

Clinical and biochemical data were obtained by reviewing medical records of all patients. All patients underwent computed tomography and/or magnetic resonance tomography of the brain. To identify the potential mechanism of cerebral infarction, electrocardiography, chest echocardiography, carotid ultrasonography, complete blood count, and blood biochemistry were performed in all patients. When indicated, some patients also underwent magnetic resonance tomography, computed tomography and/or digital subtraction angiography, transesophageal echocardiography, Holter monitoring, and special anticoagulation tests.

Arterial hypertension was considered present when the patients were on antihypertensive treatment on admission or when hypertension was diagnosed by repeated measurements of systemic blood pressure (BP) more than 140/90 mm Hg during hospital stay. Diabetes mellitus was considered present when patients had a known diagnosis and/or were on antidiabetic treatment on admission or had a fasting HbA1c value of 6.5% or more.[13] Atrial fibrillation was considered present when mentioned in patients' medical history or detected during the investigation period. Angina was considered present when mentioned in patients' medical history. All patients smoking any kind of tobacco on a daily basis were coded as smokers, whereas former smokers of at least 3 months without smoking were coded as nonsmokers. Measurements of systolic and diastolic BP and body mass index (BMI) on admission are reported. All patients were classified according to the Causative Classification of Stroke system, a computerized algorithm of Stop Stroke Study–Trial of Org 10172 in Acute Stroke Treatment system,[14] and according to ASCO (A: atherosclerosis, S: small vessel disease, C: cardiac source and O: other cause) phenotypic classification system.[15] Large artery atherosclerosis (LAA), cardioembolic (CE) etiology, small artery occlusion, and cryptogenic disease (CRYPT) comprise the main subgroups reported here. CRYPT by Trial of Org 10172 in Acute Stroke Treatment comprised patients with unidentified cause despite complete work up, and CRYPT by ASCO comprised patients with grade 0 or 3 in all pathologies.

Statistical Analysis

Baseline characteristics were compared with chi-square test for categorical variables, *t* test for normally distributed continuous variables (age, systolic and diastolic BP, BMI, white blood cell count after exclusion of 5 individuals with values over 15×10^9/L, total and LDL cholesterol levels, and hemoglobin), and Wilcoxon–Mann–Whitney test for non-normally distributed variables (admission National Institutes of Health Stroke Scale [NIHSS] score, plasma glucose, and homocysteine). Logistic regression analysis was performed to assess the risk of death at 1 month from IS onset. Univariate analysis was performed for all variables that differed significantly between survivors and deceased patients. Bonferroni